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EXAMINER

HELMS, LARRY RONALD

ART UNIT

PAPER NUMBER

1642

DATE MAILED: 08/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	10/053,530	Applicant(s)	LEDBETTER ET AL.
Examiner	Larry R. Helms	Art Unit	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 07 June 2004.
2a) This action is **FINAL**. 2b) This action is non-final.
3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1,2,4-13,19 and 23-142 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) Claim(s) _____ is/are allowed.
6) Claim(s) 1,2,4-13,19 and 23-142 is/are rejected.
7) Claim(s) _____ is/are objected to.
8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____.

DETAILED ACTION

1. Claims 1, 4, 10-11, 23-27, 32-39, 42-44, 46, 48-51, 53-55, 59, 64-71, 107-108

have been amended.

Claims 110-142 have been added.

Claims 3, 14-18, 20-22 have been canceled.

2. Claims 1-2, 4-13, 19, 23-142 are pending and under examination.
3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action
4. The following Office Action contains some NEW GROUNDS of rejection.

Claim Objections

5. Claims 136 and 138 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend on a multiple dependent claim. See MPEP § 608.01(n).

Rejections Withdrawn

6. The rejection of claims 1, 2, 5, 7-11, 19, 24-28, 31-34, 39, 50-51, 59, 72-74, 84-87, 93-94, 97 under 35 U.S.C. 102(b) as being anticipated by Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) is withdrawn in view of the amendments to the claims.

7. The rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) and further in view of Bodmer et al (U. S. Patent 5,677,425, issued 10/14/97) is withdrawn in view of the amendments to the claims. It is noted that Bodmer is not needed to meet the limitations of the claims with Shan and Shan is only needed and maintained in the 102(b) rejection below.

8. The rejection of claims 23, 26-109 under 112 first paragraph are withdrawn in view of amendments and arguments.

9. The rejection of claims under 35 USC 103(a) as being unpatentable over Shan et al in view of Kucherlapati et al is withdrawn in view of the amendments to the claims. It is noted that Kucherlapati is not needed to meet the limitations of the claims with Shan and Shan is only needed and maintained in the 102(b) rejection below.

Response to Arguments

10. The rejections of claims 1-2, 4-13, 19, 50-101, 109-141 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The response filed 6/7/04 has been carefully considered but is deemed not to be persuasive. The response states that the word "derived" reads in conjunction with the word "mutated" and refers to sequence differences in the number of cysteines or sequence changes relative to the wild-type hinge region (see pages 31-32 of the

response). In response to this argument, claim 1 for example recites “derived from a wild-type human IgA region polypeptide” wherein the hinge region is not recited as being “derived from a wild-type human IgA hinge region” as argued in the response. In addition, claims 6 and 7 recited variable region polypeptides which are “derived” from human immunoglobulins or CH3 constant regions which are “derived” from a human immunoglobulin heavy chain and have nothing to do with the hinge region in the explanation of the term “derived” in the response which only addresses the term in relation to the hinge cysteines.

11. The rejection of claims 78, 82, 98 are rejected under 35 U.S.C. 102(b) as being anticipated by Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7).

The response filed 6/07/04 has been carefully considered but is deemed not to be persuasive. The response states that claim 1 has been amended to remove the clause “that contains no cysteine residues” and thus the art of Shan does not read on the claims (see page 32-33 of response). In response to this argument, claims 78, 82, 98 require that the hinge region have no cysteines which is taught by Shan. Therefore, the art reads on the claims.

12. The rejection of claims 40-41, 43-48, 52-54, 99, 101-102 under 112 first paragraph for lacking deposit of the biological material 2H7, L6, HD37, G28-1 is maintained.

The response filed 6/7/04 has been carefully considered but is deemed not to be persuasive. Upon further consideration claims to 2H7 scFv and 1F5 are now included. The response states that the heavy and light chain variable regions for the antibodies are either in the specification in Examples 1 or in US Patent 5,354,847 (see page 36 of response). In response to this argument, it is still not clear if the single chain antibodies claimed have the sequences stated in either the specification or the patent. The claims are for "a" 2H7, L6, HD37, G28-1 or 1F5 single chain Fv. Are the antibodies claimed those which are in the specification or patent? There is no correlation besides the laboratory designations in the claims with the claimed antibodies and those in the patent or the specification. There are no SEQ ID NOs for the antibodies or ATCC or accession numbers. Since the claims are to "a" single chain antibody it is unclear if the claims are to other antibodies or only those having a specific sequence in the heavy or light chain and the rejection is maintained and made again.

13. The rejection of claim 53 under 112 first paragraph is maintained.

The response filed 6/7/04 states that the MPEP 2173.05 recites *In re Johnson* in support for a negative limitation (see page 39-41 of response). In response to this argument, Johnson listed the genus of species and then excluded one. In this case the genus has not been disclosed and is numerous in the number of antibodies that bind CD20 and not disclosed in the specification. It appears that only 2H7 and 1F5 are the antibodies disclosed in the specification but the claims encompass any antibody that

binds to CD20. The analysis of Johnson is not applicable to claim 53 and that which is disclosed in the specification.

14. The rejection of claims 107-108 under 112 first paragraph is maintained.

The response filed 6/7/04 has been carefully considered but is deemed not to be persuasive. The response states that the recitation of "any hinge peptide or polypeptide that occurs naturally" is support on page 2-23 of the specification and this includes the IgE hinge (see page 42 of response). In response to this argument, there is no support for the limitation of an IgE hinge. The analysis is compared to a claim of a specific protein and the specification has a statement that "any protein can be used in the invention". Thus according the analysis in the response, just because the specification states that any hinge can be used it supports an IgE hinge. The specification only describes IgG and IgA hinges. This is not persuasive and the rejection is maintained.

The following are NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

15. Claims 1-2, 4-13, 19, 23-142 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1, 23, 24, 25 and those depended from claims 1, 3, 24, 25, are indefinite because are the binding domain polypeptide or the single chain protein joined

directly to the hinge or can some peptide or amino acid residue be in between as a linker?

- b. Claims 35-38 recites the limitation "said single chain Fv" in claim 25. There is insufficient antecedent basis for this limitation in the claim.
- c. Claim 5 recites the limitation "binding domain Fv-immunoglobulin fusion protein" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

17. Claims 1-2, 4, 7-8, 19, 135-138, are rejected under 35 U.S.C. 102(b) as being anticipated by Bodmer et al (U. S. Patent 5,677,425, issued 10/97).

The claims recite a mutated binding domain and a hinge region that contains one cysteine from a IgG1 and CH2 and CH3 are human and from IgG and the VH and VL is from a human immunoglobulin, and a reduced ability to dimerize and a pharmaceutical

composition, and the a Ka of 10^7 M⁻¹. because of the indefinite nature of claim 1 wherein it is not clear if the binding domain is fused directly to the hinge or can have other sequences, the claim is interpreted as a binding domain fused to a hinge with a CH1 domain fused to a hinge with the heavy chain fused to the CH1 and the heavy chain is part of a binding domain.

Bodmer et al teach an antibody wherein the hinge region is modified to have one cysteine and the variable regions and the constant regions can be humanized (see column 1, lines 25-33 and column 3, lines 14-67). Since the hinge has only one cysteine it would be inherent that it would have a reduced ability to dimerize and since the fusion protein has the hinge, CH2 and CH3 it is inherent that the protein has complement fixation or dependent cell-mediated cytotoxicity.

Although the art does not teach the Ka of the affinity claimed in claims 135-136 it is the examiners position that the antibody fusion protein of Bodmer would have the claimed properties. One of ordinary skill in the art would reasonably conclude that Bodmer's antibody also possesses the same structural and functional properties as those of the antibodies claimed and, therefore, it appears that Bodmer have produced antibodies that are identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed binding protein with the protein of Bodmer, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed protein and the protein of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

18. Claims 1-2, 4-5, 6-8, 12, 19, 110, 129, 135-138 are rejected under 35 U.S.C. 102(e) as being anticipated by Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01).

The claims are summarized as a binding domain-immunoglobulin or a single chain Fv comprising a mutated hinge region that contains one cysteine from a IgG1 or has a human IgA hinge and CH2 and CH3 are human and from IgG and the VH and VL is from a human immunoglobulin, and a reduced ability to dimerize and evaluated by biochemical separation before and after reduction and a pharmaceutical composition, and the a Ka of 10 to the 7 M-1.

Gillies et al teach fusion protein of binding molecules fused to the hinge and the hinge can be modified to have only one cysteine or be from an IgG1 or IgA and the CH2 and CH3 are human and the binding domain can be a single chain Fv or a binding molecule (see Figure 2A, paragraph 0015, 0022, 0026-0034).

Although the art does not teach the Ka of the affinity claimed in claims 135-136 it is the examiners position that the antibody fusion protein of Gillies would have the claimed properties. One of ordinary skill in the art would reasonably conclude that Gillies' antibody also possesses the same structural and functional properties as those of the antibodies claimed and, therefore, it appears that Gillies have produced antibodies that are identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed binding protein with the protein of Gillies, the burden of proof is upon the Applicants to show a

distinction between the structural and functional characteristics of the claimed protein and the protein of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Claim Rejections - 35 USC § 103

19. Claims 1-2, 4-5, 6-12, 19, 50-51, 55-56, 59, 64-66, 68-69, 72-79, 82, 84-98, 109-113, 117-119, 129-138 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01) and further in view of Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) and Bodmer et al (U. S. Patent 5,677,425, issued 10/97).

The claims not described above are summarized as the binding domain binds CD20 for treatment of B-cell disorder and is a single chain Fv has a GLY linker, or an altered IgG2 hinge or has less cysteine residues than naturally, and the hinge has no cysteines, and the hinge has about 20-30 amino acids, and the variable regions are human or humanized. For this rejection the intended use recited in claim 50 for use in treatment is given no patentable weight.

Gillies et al has been described supra. Gillies et al does not teach a single chain binding to CD20 or a humanized VH and VL. These deficiencies are made up for in the teachings in Shan et al and Bodmer et al.

Shan et al teach single chain antibodies with altered hinge regions and the antibody binds CD20.

Bodmer et al has been described supra and also teach humanized VH and VL.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used an antibody to CD20 and humanize it in view of Gillies et al , Shan et al, and Bodmer et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used an antibody to CD20 and humanize it in view of Gillies et al , Shan et al, and Bodmer et al because Gillies et al teach the antibody fusions can be used for therapy and in view of Shan et al who teach the anti-CD20 binding molecule is used in therapy to treat lymphoma, it would have been obvious to substitute the binding regions of antibody of Gillies for that of Shan et al. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used an antibody to CD20 and humanize it in view of Gillies et al , Shan et al, and Bodmer et al because Bodmer et al teach humanization of the VH and VL and in view of Shan it would have been obvious to humanize the antibody for treatment in humans.

Although the art does not teach the Ka of the affinity claimed in claims 135-136 it is the examiners position that the antibody fusion protein of Gillies in view of Bodmer and Shan would have the claimed properties. One of ordinary skill in the art would reasonably conclude that Gillies in view of Bodmer and Shans antibody also possesses the same structural and functional properties as those of the antibodies claimed and,

therefore, it appears that Gillies in view of Bodmer and Shan have produced antibodies that are identical to the claimed antibody. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed binding protein with the protein of Gillies in view of Bodmer and Shan, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed protein and the protein of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced from the references.

Conclusion

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

22. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is 703-872-9306.

Larry R. Helms
571-272-0832



LARRY R. HELMS, PH.D
PRIMARY EXAMINER